

BS

MS Contin is Unequalled...

■ Unequalled
Bioavailability...

Unequalled
Effectiveness...

Unequalled
Experience...


MS Contin® 
(morphine sulfate 30 mg
controlled-release) tablets

Trial Exhibit

Purdue et al. v. Endo et al.
Nos. 00 Civ. 8029 (SHS);
01 Civ. 2109 (SHS); 01 Civ. 8177 (SHS)

DX 3260**Deposition Exhibit**

Purdue et al. v. Endo et al.
Nos. 00 Civ. 8029 (SHS);
01 Civ. 2109 (SHS); 01 Civ. 8177 (SHS)

DX 694**P 041765**6/19/02 

Unequalled Bioavailability...

■ MS Contin has superior 12-hour bioavailability:

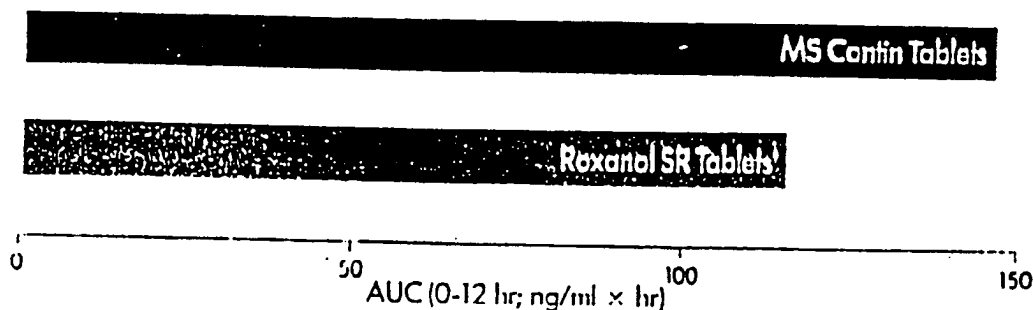
MS Contin is 27% more bioavailable than Roxanol SR.

Bioavailability:

"The extent to which a drug reaches its site of action or a biological fluid from which the drug has access to its site of action."

(Goldman and Gilman's The Pharmacology of Drugs at Therapeutic Doses, Edited by Alfred Goldman et al. (7th ed.) New York: Macmillan, 1985, p. 1)

Bioavailability (0-12 hr) of MS Contin 30 mg Tablets vs. Roxanol SR 30 mg Tablets as determined by plasma drug levels in a crossover study in 18 normal volunteers



Important Note: While there is an indirect relationship between plasma morphine levels and analgesia, higher plasma levels are generally associated with superior relief of pain, as demonstrated in the literature. There is a lag time or hysteresis between the time of peak plasma morphine levels and the time of peak drug effects.

MS Contin 30 mg Tablets are a Schedule II controlled substance. Roxanol SR 30 mg Tablets are a Schedule II controlled substance. Both are potent analgesics and should be used with caution. For more information, see the full prescribing information for each product. © 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 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MS Contin[®] (morphine sulfate 30 mg controlled-release) tablets

- No other morphine product is bioequivalent to MS Contin.
- MS Contin and Roxanol SR are not bioequivalent, therefore, Roxanol SR is not therapeutically interchangeable with MS Contin.^{†,††}
- MS Contin reaches a significantly higher peak concentration, for more effective analgesia.

Bioequivalence:

"They [pharmaceutical formulations] are said to be biologically equivalent if they yield similar concentrations of drug in blood and tissues...Pharmaceutical preparations that are chemically equivalent but not biologically or therapeutically equivalent are said to differ in their bioavailability."

Continued from Volume 1, page 10

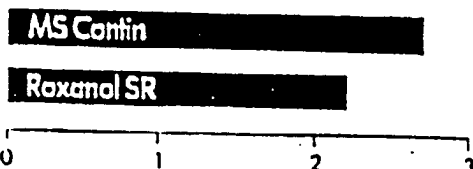
The three criteria for bioequivalency are comparable...

1. bioavailability (calculated from area under the time-concentration-curve)
2. time to peak plasma concentration
3. peak concentration

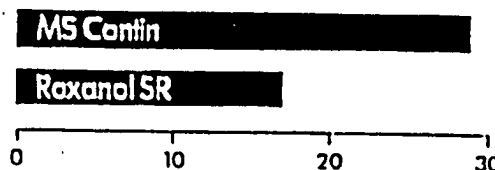
Results of Comparative Study[†]

	MS Contin (2 x 30 mg)	Roxanol SR (2 x 30 mg)
AUC	147 (0-12 hr; ng/ml x hr)	116
T _{max} (hrs)	2.7	2.2
C _{max} (ng/ml)	29	17

Time to Peak Concentration (T_{max})[†]



Peak Concentration (C_{max})[†]



^{††} See MS Contin Comparative Bioequivalency of Two Controlled-Release Morphine Tablets. Accepted for presentation at the Sixth Annual Meeting of the American Pain Society, Washington, D.C., Nov. 1995.
^{†††} See MS Contin Comparative Bioequivalency of Controlled-Release Oral Morphine Tablets for Long- vs. Short-Acting Analgesia. Accepted for presentation at the 38th World Conference on Clinical Pharmacology and Therapeutics, Stockholm, Sweden, September 1995.

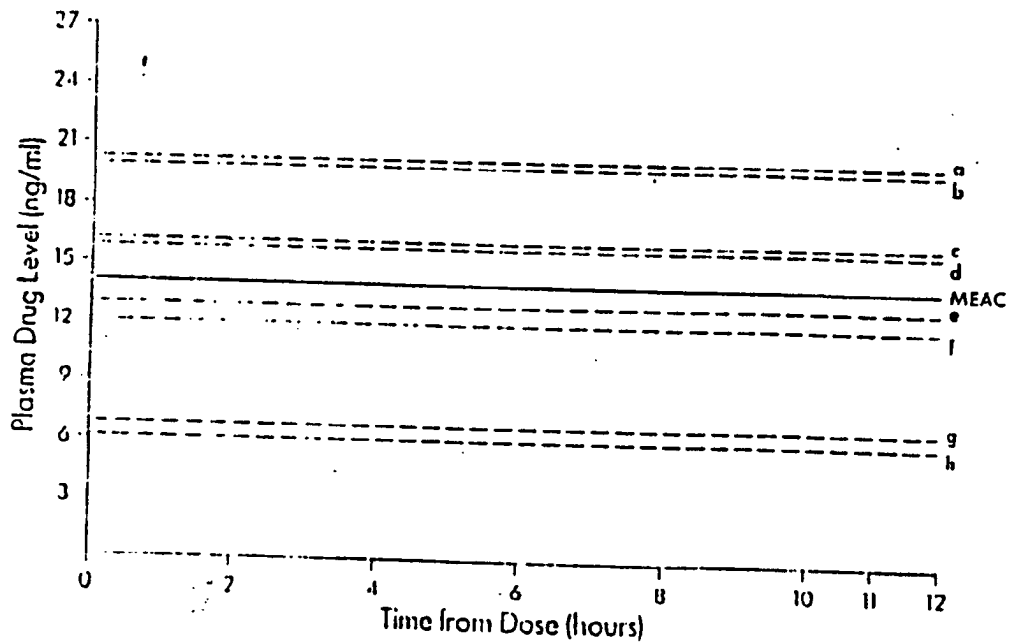
Proven Against Cancer Pain

Unequalled Effectiveness...

What is the effective analgesic level of oral morphine?

A careful review of the literature^{a-h} indicates the complexity of defining effective analgesic plasma morphine levels. However, there is generally a "Minimally Effective Analgesic Concentration" (MEAC) of plasma morphine below which no analgesia is provided (see Chart below).

Minimally Effective Analgesic Concentrations (MEAC) of Morphine



References: a) J. Clin. Pharmacol. 1984; 24: 100-105. b) J. Clin. Pharmacol. 1984; 24: 106-110. c) J. Clin. Pharmacol. 1984; 24: 111-115. d) J. Clin. Pharmacol. 1984; 24: 116-120. e) J. Clin. Pharmacol. 1984; 24: 121-125. f) J. Clin. Pharmacol. 1984; 24: 126-130. g) J. Clin. Pharmacol. 1984; 24: 131-135. h) J. Clin. Pharmacol. 1984; 24: 136-140.

12-Hour MS Contin[®]...

Unequalled Experience...

- Extensive published clinical documentation that supports 12-hour efficacy and safety¹⁻¹⁴
- Over 6 years' proven clinical experience with over a half-million prescriptions¹
- MS Contin has a clinically documented safety profile:
In over 95% of patients, side effects were fewer or equal to pre-study analgesic¹⁵⁻¹⁷

Percent of patients experiencing fewer or equal side effects¹⁵⁻¹⁷

Study #1: Memorial Sloan-Kettering Cancer Center

55% of patients experienced fewer side effects
21% of patients experienced equal side effects

Study #2: New York University School of Medicine

91% of patients experienced fewer side effects
6% of patients experienced equal side effects

Study #3: Bowman Gray School of Medicine

52% of patients experienced fewer side effects
48% of patients experienced equal side effects

117,000 prescriptions reported in clinical pharmacology on LRI (1988-94) and on LISA (1994)

12-Hour MS Contin[®]...

MS Contin[®] (morphine sulfate 30 mg controlled-release) tablets

- **MS Contin is the subject of two international symposia on pain control.¹⁸⁻¹⁹**
- **Safety and efficacy demonstrated at prestigious cancer treatment centers in over 1200 study patients.**
- **Professional educational support:**
Speakers' Bureau; Educational Slides and Videotapes, including "Cancer Pain Management" Chaired by Dr. Kathleen M. Foley of Memorial Sloan-Kettering Cancer Center.
- **MS Contin Tablets are small, round and film coated.**
Their distinctive lavender color makes them easy to recognize and identify.
Their small size (less than half that of Roxanol SR) makes them easy to swallow.



References: 1. Harrison et al. and Harrison, J. Controlled evaluation and ongoing trial of continuous subcutaneous morphine in patients with advanced cancer. Presented at the 1982 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1982. 2. Harrison GW and Harrison J. Controlled release morphine tablets are effective in long-term study design relieving severe pain. Presented at the 1982 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1982. 3. Walsh TD. Clinical evaluation of new release morphine tablets. Advances in Pain Research and Therapy 9:727-731, 1985. 4. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 5. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 6. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 7. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 8. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 9. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 10. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 11. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 12. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 13. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 14. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 15. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 16. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 17. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 18. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 19. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984.


Proven Against Cancer Pain

MS Contin[®] is Unequaled...

The only 12-hour oral narcotic analgesic proven against cancer pain.

- Superior 12-hour bioavailability – 27% more bioavailable than Roxanol SR.
- No other morphine product is bioequivalent to MS Contin; therefore, none is therapeutically interchangeable.
- Achieves a significantly higher peak concentration – for more effective analgesia.
- Maintains plasma morphine levels above the minimally effective analgesic concentration (MEAC) significantly longer – for effective pain relief.
- Published clinical documentation of superior or equal efficacy compared to immediate-release morphine and other oral opioid analgesics.
- Proven safety profile – published clinical documentation shows fewer side effects than previous analgesic (Hydromorphone, Methadone, Oxycodone, Codeine, Meperidine).

Also available

MSIR[™] Useful in starting patients on morphine or for treating breakthrough or incident pain.
(morphine sulfate) 15 mg and 30 mg Immediate-Release Tablets 

12-hour MS Contin[®] 
(morphine sulfate 30 mg controlled-release) tablets

**Proven Against
Cancer Pain**

For Prescribing Information Please See Accompanying Professional Literature

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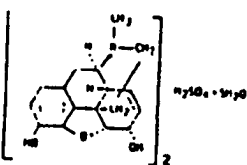
MS CONTIN® 30 mg Tablets
MS CONTIN® 60 mg Tablets
MS CONTIN® 100 mg Tablets
Morphine Sulfate
Controlled Release

WARNING: May be habit forming.

... 23220

DESCRIPTION:

Chemically, morphine sulfate is 7,8-dihydro-4,5-epoxy-17-methylmorphine-3- β -D-glucopyranoside (2:1 ratio) pentahydrate and has the following structure (1):



Each MS CONTIN 15 mg Controlled Release Tablet contains: 15 mg Morphine Sulfate U.S.P. inactive ingredients: Croscarellulose, Hydroxypropyl Methylcellulose, Lactose Monohydrate, Magnesium Stearate, and other ingredients.

Each MS CONTIN 30 mg Controlled Release Tablet contains: 30 mg Morphine Sulfate U.S.P. inactive ingredients: Croscarellulose, Hydroxypropyl Methylcellulose, Lactose Monohydrate, Magnesium Stearate, and other ingredients.

Each MS CONTIN 60 mg Controlled Release Tablet contains: 60 mg Morphine Sulfate U.S.P. inactive ingredients: Croscarellulose, Hydroxypropyl Methylcellulose, Lactose Monohydrate, Magnesium Stearate, and other ingredients.

Each MS CONTIN 100 mg Controlled Release Tablet contains: 100 mg Morphine Sulfate U.S.P. inactive ingredients: Croscarellulose, Hydroxypropyl Methylcellulose, Lactose Monohydrate, Magnesium Stearate, and other ingredients.

CLINICAL PHARMACOLOGY:
Pharmacokinetics and Pharmacodynamics
 MS CONTIN is a controlled release tablet containing morphine sulfate. Following oral administration of a given dose of morphine, the amount of morphine absorbed is proportional to the dose. Morphine is converted to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in the liver. M3G is inactive, while M6G is active and contributes to the analgesic effect. The elimination half-life of morphine is approximately 3-4 hours.

Once absorbed, morphine is distributed to various tissues. It is metabolized in the liver to M3G and M6G. The elimination half-life of morphine is approximately 3-4 hours. The elimination half-life of M3G is approximately 10-12 hours, and the elimination half-life of M6G is approximately 10-12 hours.

Although a small fraction (less than 1%) of morphine is excreted unchanged in the urine, the majority of morphine is converted to M3G and M6G. The elimination half-life of morphine is approximately 3-4 hours. The elimination half-life of M3G is approximately 10-12 hours, and the elimination half-life of M6G is approximately 10-12 hours.

The pharmacologic system has a very high capacity and is not easily saturated. The rate of elimination of morphine is proportional to the dose. The elimination half-life of morphine is approximately 3-4 hours. The elimination half-life of M3G is approximately 10-12 hours, and the elimination half-life of M6G is approximately 10-12 hours.

The following pharmacokinetic parameters show considerable inter-subject variation. The pharmacokinetic parameters of morphine are: elimination half-life (3-4 hours), elimination half-life of M3G (10-12 hours), and elimination half-life of M6G (10-12 hours).

Following the administration of controlled release morphine products, approximately 80% of the morphine that is released from the tablet is absorbed. The elimination half-life of morphine is approximately 3-4 hours. The elimination half-life of M3G is approximately 10-12 hours, and the elimination half-life of M6G is approximately 10-12 hours.

The pharmacokinetic parameters of morphine are: elimination half-life (3-4 hours), elimination half-life of M3G (10-12 hours), and elimination half-life of M6G (10-12 hours). The elimination half-life of morphine is approximately 3-4 hours. The elimination half-life of M3G is approximately 10-12 hours, and the elimination half-life of M6G is approximately 10-12 hours.

When the pharmacokinetic parameters of morphine are compared to those of morphine sulfate, the elimination half-life of morphine is approximately 3-4 hours. The elimination half-life of M3G is approximately 10-12 hours, and the elimination half-life of M6G is approximately 10-12 hours.

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The elimination of morphine occurs primarily via renal excretion of 3-morphine glucuronide. A small amount of the pharmacologic activity is excreted in the bile, and there is some enterohepatic recirculation. Bile acids are primarily metabolized to inactive glucuronides, and the effects of renal disease on morphine's elimination are not likely to be pronounced. However, in elderly patients, caution should be taken to avoid potential accumulation of renal excreted metabolites.

PHARMACODYNAMICS:
 The effects described below are common to all morphine-containing products.

Central Nervous System
 The principal actions of morphine are analgesia and sedation (e.g., euphoria and anxiolysis).

The precise mechanism of the analgesic action is unknown. However, morphine acts on receptors and subsequent components with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the perception of nociceptive stimuli.

Morphine produces respiratory depression by direct action on brain stem respiratory centers. The mechanism of respiratory depression involves a reduction in the ventilatory response to carbon dioxide retention, and is enhanced by hypoxia.

Morphine decreases the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Morphine causes miosis, even in total darkness. Pupillary miosis is a sign of central depression but is not pathognomonic. In a patient with a history of glaucoma or other eye disease, morphine may produce a myopic shift. Myopic shift is more likely to occur with doses higher than those usually required for analgesia.

Cardiovascular and Other Smooth Muscle
 Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in tone in the smooth muscle of the gastrointestinal tract. Depression of tone in the smooth muscle of the gut and the consequent decrease in peristalsis may lead to constipation. Prolonged constipation may lead to abdominal discomfort, which may be relieved by the use of laxatives. The anal effect of morphine is a result of its action on the smooth muscle of the gut.

Cardiovascular System
 Morphine produces peripheral vasodilation which may result in orthostatic hypotension. Reduction of venous return may occur and may contribute to decreased cardiac output. Manifestations of hypotension include hypotension, tachycardia, and possibly pulmonary edema. Morphine may also cause peripheral vasodilation which may include flushing, redness, and itching.

INDICATIONS AND USAGE:
 MS CONTIN is a controlled release tablet containing morphine sulfate for the relief of moderate to severe pain. It is indicated for use in patients who require repeated doses of morphine sulfate for the relief of moderate to severe pain.

CONTRAINDICATIONS:
 MS CONTIN is contraindicated in patients with known hypersensitivity to the drug, to patients with respiratory depression in the absence of adequate ventilation, and to patients with acute or severe bronchial asthma. MS CONTIN is contraindicated in any patient who has or is suspected of having a paralytic ileus.

WARNINGS: (See also CLINICAL PHARMACOLOGY)

Impaired Respiration
 Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs most frequently in the elderly and debilitated patient as well as in those suffering from conditions accompanied by hypoxia or hypoxemia. When such conditions are present, morphine may cause respiratory depression.

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or the pulmonary, and in patients having a substantially decreased respiratory reserve. In such patients, even small therapeutic doses of morphine may decrease respiratory drive while paradoxically increasing drive by stimulating the pain of apnea.

Head Injury and Increased Intracranial Pressure
 The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or pre-existing increases in intracranial pressure. Morphine produces effects which may obscure neurologic signs of further increases in pressure in patients with head lesions.

Hypotension (Shock)
 MS CONTIN may cause hypotension. Morphine lowers blood pressure in an individual whose ability to maintain blood pressure has already been compromised by a reduced blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics. (See also PRECAUTIONS, Drug Interactions.) MS CONTIN may produce orthostatic hypotension in ambulatory patients.

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Respiratory depression, hypotension and hypoxemia should not be administered to a patient who has received or is receiving a narcotic therapy with a high degree of tolerance. In these patients, even hypotension/hypoxemia may result in the hypoxemic effect of the hypotension without symptoms.

Drug Dependence
 Morphine can produce drug dependence and has a potential for abuse. Abuse of morphine may lead to psychological and physical dependence. Abuse of morphine may lead to psychological and physical dependence. Abuse of morphine may lead to psychological and physical dependence.

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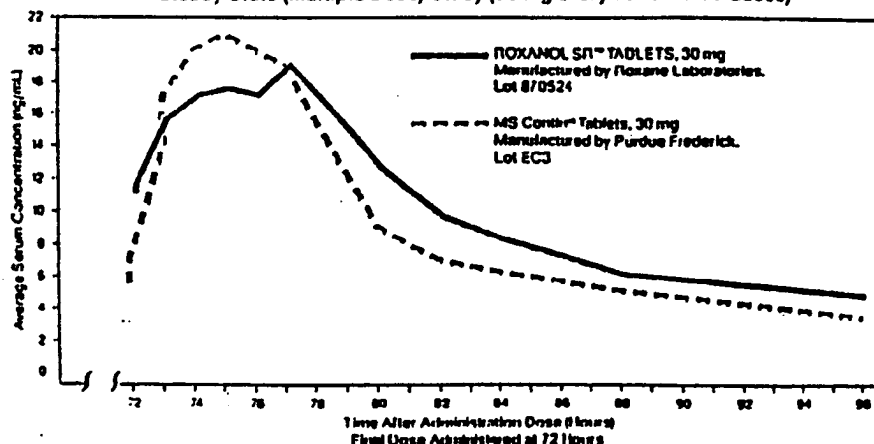
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**AVERAGE SERUM CONCENTRATIONS OF
MORPHINE FOR ROXANOL SR™ TABLETS AND MS CONTIN® TABLETS**
Steady State (Multiple Dose) Study (30 mg every 12 hours x 7 doses)



Time After Administration (hours)
Final Dose Administered at 72 hours
Adapted from Abstracts of the 1988 American Society of Clinical Oncologists Meeting

Multiple-dose randomized crossover trial
demonstrates Roxanol SR and MS Contin
are bioequivalent.

□ Evaluations of standard pharmacokinetic parameters (AUC 72-96 hr, AUC 72-84 hr, Cmax and Cavg) showed less than 10% difference between the two sustained release morphine treatments.

□ The investigators concluded that Roxanol SR is bioequivalent to MS Contin.

**More cost-effective
than MS Contin**

□ Roxanol SR offers greater cost containment benefits for hospitals.*

□ Roxanol SR is a greater value for patients who need relief of chronic cancer pain.*

*Based on 1988 National prices

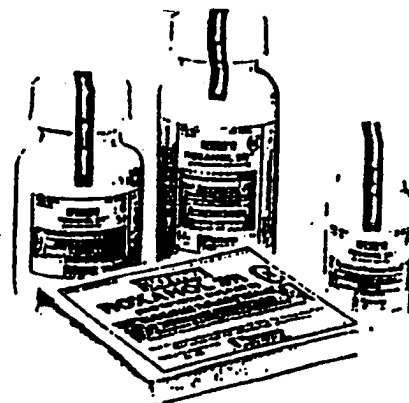
ROXANOL SR™ Tablets @
(Morphine Sulfate Sustained Release Tablets)

WARNING: May be habit forming.

Dosing and Administration

The patients should first be stabilized on Roxanol Concentrated Oral Solution. Convert to Roxanol SR by dividing the total daily Roxanol requirement (in milligrams) by three and administering as Roxanol SR Tablets every eight hours. The dose and dosage schedule can be adjusted for greater flexibility according to severity of pain as well as for the patient's underlying disease, age, and size.

Tablets must be swallowed whole...not broken, crushed, or chewed. Tablets have a methyl cellulose coating for easier swallowing.

[illegible]